200 and 300 yards. The patient is very worn and tired from severe rest-pain. On the right side there is a feeble pulse to apex of Scarpa's triangle, but the femoral artery is felt as a solid cord below this point. On the left side all pulses present, but very weak. Operation: transperitoneal excision right and left lumbar cords, July 4th, 1932. Temperature rose on right 0.6° C. and on left 5° C. This man walks well and is free from pain, excepting a slight cramp of the right calf if he hurries. His general condition is greatly improved. Result classified as "good."

15. E. W., aged 31 years, chemist. History eight months. Began with claudication of left calf and thrombo-phlebitis of internal saphenous vein. All pulses in each leg are so feeble as to be doubtful, excepting the common femoral, which is strong on both sides. Operation: transperitoneal excision right and left lumbar cords, December 12th, 1931. Temperature rose on right 1.8° C. and on left 0.8° C. He is now free from pain, "can walk miles," and is playing cricket. He has, three months after the operation, developed Raynaud's disease of both hands. Result classified as "good."

16. J. W., aged 55 years, taxi-owner. History of sixteen years. Began with pain in left calf. Has got steadily worse and now has claudication at 200 yards. Has had onychia of first toe of left foot for two years. A callous ulcer has been present the whole of this time. There is much rest-pain. All pulses were perceptible in right leg, but no pulse was felt in left leg, excepting good common femoral. Operation: extraperitoneal excision of left lumbar cord, August 8th, 1932. Temperature rose on right 4° C. and on left 2.8° C. There was immediate improvement in the condition of the left foot. The ulcer healed quickly. Result classified as "good."

EFFECT OF PASSAGE THROUGH GLOSSINA ON THE RESISTANCE OF A TRYPARSAMIDE-FAST TRYPANOSOME*

BY

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In previous papers (1930-2) we have shown that if laboratory animals infected with a pathogenic trypanosome are treated with appropriate doses of an aromatic arsenical or antimonial compound—for example, atoxyl, tryparsamide, arsacetin, neosalvarsan, stibenyl, etc.—strains possessing a high degree of "drug resistance" (or "drug fastness") are produced. These various resistant strains are similar in that each is resistant not only to the drug used to produce it, but also, broadly speaking, to all the other aromatic arsenical or antimonial compounds commonly employed in the therapy of trypanosomiasis, and also to the acridine dye, acriflavine; but each is just as sensitive to the non-aromatic compounds of arsenic (sodium arsenite) and antimony (tartar emetic) and to "Bayer 205" as is the normal parent strain. For example, an atoxyl-fast strain is resistant not only to atoxyl, but also to arsacetin, orsanine, tryparsamide, halarzol, salvarsan, stibenyl, and acriflavine; but it is normally sensitive to sodium arsenite, to tartar emetic, and to "Bayer 205." If the resistant strains are passaged through mice the resistant character is preserved unchanged for prolonged periods. Our atoxyl-fast strain has been passaged through a series of 280 mice since it was last exposed (in August, 1930) to the action of any drug, and it is still as resistant to atoxyl and other aromatic arsenicals as it was two and a half years ago.

* This work was assisted by a grant from the Chemotherapy Committee of the Medical Research Council.

Contrary to the generally accepted view, we have found that the resistant character of a trypanosome is not modified by transference of the parasite from one vertebrate host to another. A strain of trypanosomes made resistant by treating infected mice or rabbits with atoxyl or tryparsamide retains its resistance when transferred to other hosts. In short, it appears that resistance to the aromatic arsenicals is a stable character, which is inherent in the trypanosomes themselves; it persists unchanged for prolonged periods when the parasite is passaged through laboratory animals, and it is in no way modified by changing the vertebrate host. Finally, no method has as yet been discovered whereby the acquired resistant character can be destroyed: our attempts to confirm Citron's (1930) statement that salvarsan resistance can be removed by sodium thiosulphate have been fruitless.

DRUG RESISTANCE OF TRYPANOSOMES IN MAN

Apart from its academic interest, the problem of drug resistance is a matter of immediate practical importance in so far as it probably has a very important bearing on the treatment of human trypanosomiasis. When once a strain of trypanosomes has attained to a certain degree of atoxyl- or tryparsamide-resistance it is impossible to cure any laboratory animal infected with that strain by the administration of even maximum doses of any aromatic compound of arsenic or antimony. If a resistant strain is developed in the course of arsenical treatment of a human case of trypanosomiasis (and as such strains can be produced in the treatment of infected mice, rats, guinea-pigs, or rabbits with equal facility there seems no reason to doubt that under suitable conditions they will likewise develop in man), then from analogy of the laboratory observations it will prove a hopeless task to attempt to cure such a patient with any aromatic arsenical or antimonial compound. An examination of the factors (size of dose, frequency and number of doses, etc.) which govern the production of drug resistance in trypanosomal infections of animals and man is consequently a matter of first importance.

That a drug-resistant strain of trypanosomes retains its resistant character, not only throughout the life of the host in which it first becomes resistant, but also throughout the lives of hundreds of other hosts through which it is passaged by means of direct inoculation of infected blood, is obviously a fact of considerable importance. It is, however, of relatively little practical significance in comparison with the question whether a drug-resistant strain of trypanosomes preserves its resistant character after it has passed through its cyclical development in its intermediate host—*Glossina*.

PERSISTENCE OF DRUG RESISTANCE IN INTERMEDIATE HOST

That this fundamental problem has received very little attention is probably due to two main reasons. In the first place, ever since Kleine in 1909 discovered that *T. brucei* underwent a biological development in *G. palpalis*, there has undoubtedly been a general consensus of opinion that one of the most important results of this process was to maintain constant the pathogenicity and other biological characters of the trypanosome; it was considered that the alternate passage through the insect and vertebrate hosts which takes place in nature prevents such changes in the trypanosome as are known to develop in the parasite when it is passaged through a series of laboratory animals by means of blood inoculation. In the second place, notwithstanding the great amount of work which has been devoted to the problem of drug resistance in trypanosomes since the fundamental discovery of the phenomenon by Franke and Roehl in 1907, we have had until recently but little precise knowledge of

the subject. Not only had no method been devised for assessing the degree of drug resistance exhibited by the trypanosome, but many false conceptions, based on inadequate experimental data—for example, that drug resistance was not merely a character of the trypanosome itself, but that in some unexplained way it was dependent on the host—had so complicated and confused the subject that the investigation of the fundamental question whether drug resistance survived the biological development of the trypanosome in *Glossina* seemed a well-nigh hopeless task.

The truth of these observations is demonstrated by a critical study of the three papers which have hitherto appeared dealing with the question whether the acquired character of drug resistance survives the passage of the trypanosome through its invertebrate host. Werbitzki and Gonder (1911), working in Ehrlich's laboratory, were the first to investigate the subject experimentally. The problem they set themselves was to determine whether an arsenophenylglycine-resistant strain of *T. brucei* would develop in the rat-louse (*Haematopinus spinulosus*), and, if so, whether or not it would remain arsenic-fast. It is recorded that the normal strain of *T. lewisi* used by the authors was sensitive to doses of 0.1 gram of arsenophenylglycine per kilo of rat, and that the resistant strain, which required two years for its production, withstood doses of 0.2 gram per kilo. In various experiments it was found that, when rats were inoculated with ground-up lice which had been infected with the resistant strain for at least sixteen days, they developed an infection which was normally sensitive to arsenophenylglycine. Gonder therefore concluded that the passage of a resistant strain through the louse *Haematopinus spinulosus* caused the disappearance of its resistant character.

Ehrlich (1911), in commenting on these observations, stated that not only were they of great scientific interest in so far as they touched the question of the transmission of acquired characters and the theory of mutation, but that they were also of great practical significance. On the one hand, the chemotherapeutic treatment of infectious diseases was becoming ever wider and of greater importance, and, on the other, the development of drug-resistant strains had been observed among the various pathogenic organisms as a consequence of such treatment. These facts had given rise to an uneasy feeling that the various diseases might undergo a fundamental change of an unfavourable nature whereby, finally, drug-resistant strains of parasites would be produced and propagated; thus infections in the future would prove intractable to chemicals which previously had shown themselves to be very active. In his opinion these observations of Gonder, that acquired characters are entirely or partly lost through the processes of fertilization and insect transmission, were well calculated to allay this disquietude.

There can be no doubt that these remarks of Ehrlich have exerted a profound influence, not only on scientific thought, but also on the practical measures adopted for the combat of sleeping sickness epidemics—for example, the French method of widespread atoxylization of the sick in the bush.

Apart from other considerations there is obviously one very serious criticism of Werbitzki and Gonder's work—namely, that the louse *Haematopinus spinulosus* is not the normal intermediate host of *T. lewisi*; in fact, the work of Nöller (1914) indicates that *T. lewisi* does not undergo a biological development in the louse as it does in its normal intermediate host, the flea.

Many years later, Reichenow and Regendanz (1927) repeated the work of Werbitzki and Gonder, but used the flea instead of the louse. These workers, contrary to Werbitzki and Gonder, reached the general conclusion that passage of the trypanosome through the flea exerted no influence one way or the other on its arsenic resist-

ance. The chief difficulty in reaching any definite conclusions from Reichenow and Regendanz's work is that critical examination of their experimental data reveals the fact that there is no evidence that their so-called "resistant" strain of *T. lewisi* was substantially more resistant to arsenophenylglycine than was their normal strain—a difficulty which Reichenow and Regendanz frankly admit.

Duke (1927) is the only worker who has investigated the subject with one of the African pathogenic trypanosomes and *Glossina*. He used a strain of *T. brucei* from an antelope shot on Damba Island. His experiments consisted in endeavouring to make the strain atoxyl-resistant by treating infected monkeys with small and increasing doses of the drug, and then, after passing the strain through *Glossina*, examining the resistance of the infection in monkeys infected from the fly. Duke reached the conclusion that the acquired character of resistance of a trypanosome to arsenic persists after cyclical passage of the strain through *Glossina*. Unfortunately the same criticism applies to Duke's experiments as to Reichenow and Regendanz's. In the first place, there is no evidence that the resistance of the strain to atoxyl had actually been increased before the tsetse were infected with it. In the second place, the strain was very sensitive to atoxyl after it had been passed through *Glossina*—in fact, since such small doses as 0.02 gram and 0.025 gram per kilo of atoxyl cleared the blood of monkeys infected with the fly-transmitted strain, it would seem clear that the trypanosome was scarcely, if any, more resistant to atoxyl than it had been at the time of its isolation from the antelope. The belief that the *dosis efficax* of atoxyl for the original strain was 0.01 gram per kilo is, as the records show, quite unfounded, since no account was taken of the cumulative effect of repeated small doses.

AUTHORS' INVESTIGATIONS

In view of the great scientific and practical importance of the problem, and of the very unsatisfactory nature of previous attempts to solve it, we decided, if possible, to reinvestigate the subject. With this object we wrote to Dr. H. L. Duke of Uganda and to Dr. J. F. Corson of Tanganyika, asking them to be good enough to send by air mail regular supplies of pupae of *Glossina palpalis* and *Glossina morsitans* respectively. From Dr. Duke we have, during the past six months, received seven or eight consignments, each of about 500 pupae collected on the shores of Lake Victoria, and from Dr. Corson one large consignment of about 3,000 pupae of *G. morsitans* collected at Kikori. To both these gentlemen our thanks are due. Whilst several interesting facts have come to light in the course of our investigations, we propose in this preliminary communication to limit ourselves strictly to the main observations bearing on the question whether or not the resistance of a drug-fast trypanosome is modified by passage through *Glossina*.

Normal Strain

The trypanosome used was a strain of *T. brucei* obtained by Dr. A. R. D. Adams in South Ankole, Uganda, by exposing a dog to the bite of wild *Glossina* in April, 1931. This strain has since been maintained by passage through guinea-pigs, as is shown in Table I. The parasite is a typically polymorphic trypanosome, and exhibits numerous posterior nuclear forms. Its virulence for guinea-pigs, rats, and mice is similar to that of other recently isolated strains of *T. brucei* or *T. rhodesiense*: it kills guinea-pigs in eight to twelve weeks, and mice in four to eight weeks. Trypanosomes are usually to be found in considerable numbers in the peripheral blood of these animals throughout the course of the disease.

With the object of ascertaining the response of the normal parent strain to various arsenical compounds a number of mice and guinea-pigs were subinoculated from animals of the main-passage series—namely, guinea-pig 3b, and guinea-pigs 681E and 795b. In the present paper we shall confine

TABLE I.—Showing the History of the Parent Strain of *T. brucei* and of its Tryparsamide-resistant Branch, and the Passage of each through *Glossina morsitans*

Fly-transmitted Normal Strain	Parent Strain		Fly-transmitted Resistant Strain
	Main Stem	Tryparsamide-resistant Branch	
Mice Guinea-pig 821A† " 821B† " 821C† " 886A " 886B " 919A " 919B†	Wild <i>Glossina</i>		
	Dog ... (Passage I)		
	Guinea-pig 870 " II		
	" 121A " III		
	" 121B " IV		
	" 1A " V		
	" 2A " VI		
	" 3B† " VII		
	" 103B " VIII		
	" 103C " IX		
	" 681B " X		
	" 681C " XI	→ 681C*†	
	" 681E† " XII	Guinea-pig 946†	→ <i>G. morsitans</i> →
	" 795D† " XIII	" 966†	
	" 98A " XIV		
			Mice Guinea-pig 14B† " 14C " 62 " 67A " 67B†

* Infection made resistant by repeated doses of tryparsamide (Table II).

† From these guinea-pigs mice were inoculated to test the sensitiveness of the various strains to arsenicals.

TABLE II.—Showing the Production of the Tryparsamide-resistant Branch

Guinea-pig 681c	September		October																												November															
	21	22-29	30	1	3	4	5	6	7	8	10	11	12	13	14	15	17	18	20	21	22	24	25	26	27	28-31	1	2	3	4	5	7	8	9	10	11	12	14	15	16						
Blood infection	...	+	—	$\frac{1}{2}$	3	3	$\frac{1}{20}$	$\frac{1}{10}$	1	5	10	20	10	10	5	2	10	20	—	$\frac{1}{10}$	5	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{50}$	2	—	$\frac{1}{10}$	2	10	20	30	+	+	3	20	20	30	30	20	20	20					
Tryparsamide	...	0.125			0.04	0.04			0.04	0.04	0.06	0.08	0.1			0.15	0.2			0.15		0.15		0.2				0.15	0.2	0.2	0.5															

N.B.—Blood infection: The figures indicate the number of trypanosomes per microscope field. Tryparsamide: The figures indicate dose in grams per kilo of guinea-pig. * On this date animals were subinoculated to test the resistance of the strain to arsenicals, and the feeding of *Glossina* commenced.

ourselves to a consideration of the minimum effective doses (M.E.D.)—that is, the minimum doses per kilo of body weight of guinea-pig, or per 20 grams of mouse—which just suffice to clear the peripheral blood of parasites. The drugs used were tryparsamide, reduced tryparsamide, arsacetin, and halarsol. As will be seen from Tables III and IV the M.E.D. for the normal parent strain was: in the case of the guinea-pig, about 0.05 gram of tryparsamide per kilo; and in the case of mice about 8 mg. of tryparsamide, 4 mg. of arsacetin, 0.08 mg. of reduced tryparsamide, and 0.03 mg. of halarsol per 20 grams of mouse. These figures show that the response of this strain of trypanosomes is very similar to that of three other recently isolated strains, all of which came from men suffering from *rhodesiense* sleeping sickness. It is perhaps worthy of note that all four strains are thus rather less sensitive to arsenicals than is our old laboratory strain of *T. rhodesiense*, which, as we have stated in previous papers, has been maintained in the laboratory by passage through mice for about eight years.

Preparation of the Resistant Variety

With the object of preparing a strain resistant to arsenicals, guinea-pig 681C (after the main strain had been passed on into guinea-pig 681E) was treated with repeated small, gradually increasing doses of tryparsamide. Details are given in Table II, from which it will be seen that a stage was finally reached when a dose of 0.5 gram per kilo failed to clear the blood of parasites. As this dose approached the maximum tolerated by a guinea-pig, and as it was ten times the dose which we had found to be the M.E.D. for the normal parent strain, it was decided, at this point, to stop the administration of tryparsamide and to test the response of the strain to arsenicals in subinoculated mice and guinea-pigs. As will be seen in Tables III and IV, in the case of the guinea-pig

TABLE III.—Showing the Minimum Effective Dose of Tryparsamide for Guinea-pigs Infected with the Normal and Tryparsamide-resistant Strains respectively, before and after Passage through *G. morsitans*

	Normal Strain		Tryparsamide-resistant Strain	
	Parent	Fly-transmitted	Parent	Fly-transmitted
Tryparsamide ...	0.05	0.05	0.5+	0.5+

N.B.—The figures represent gram per kilo of guinea-pig.

TABLE IV.—Showing the Minimum Effective Dose of Various Drugs for Mice Infected with the Normal and Tryparsamide-resistant Strains respectively, before and after Passage through *G. morsitans*

	Normal Strain		Tryparsamide-resistant Strain	
	Parent	Fly-transmitted	Parent	Fly-transmitted
	Source of Infection	Source of Infection	Source of Infection	Source of Infection
	G.-pig 3A " 795D	Fly Direct G.-pig 821A " 821B " 821C	G.-pig 681C " 946 " 966	Fly Direct G.-pig 14B " 67B
Tryparsamide ...	8.0	8.0	45.0+	45.0+
Red tryparsamide	0.08	0.08	2.0+	2.0+
Arsacetin ...	4.0	4.0	30.0+	30.0+
Halarsol ...	0.03	0.03	0.6+	0.6+

N.B.—The figures represent milligrams per 20 grams of mouse.

0.5 gram of trypanamide per kilo failed to clear the blood of parasites; and in the case of the mouse 45 mg. of trypanamide, 2 mg. of reduced trypanamide, 30 mg. of arsacetin, and 0.6 mg. of halsarsol per 20 grams were similarly ineffective. It should be noted that these doses represent approximately the maximum doses of the various drugs tolerated by the majority of guinea-pigs and mice respectively. Comparison of these figures with those previously given for the normal parent strain shows that the resistant variety had thus attained to a very high degree of resistance.

Transmission through *Glossina*

Having reached this stage, we were now in a position to attempt the crucial experiment of feeding *Glossina* on animals infected with the normal parent strain and its resistant variety respectively. Accordingly, between September 26th and October 5th, 1932, ninety-one *G. palpalis* and ninety *G. morsitans* were fed on guinea-pig 681E, infected with the normal parent strain; and between November 9th and November 28th, fifty-eight *G. palpalis* and fifty-one *G. morsitans* on guinea-pigs 681C and 946, infected with the resistant variety. It is not our intention in the present communication to describe this work in detail, and we shall confine ourselves to the main issue. In three of the tsetse flies (two *G. morsitans* and one *G. palpalis*) fed on the normal parent strain the trypanosomes passed through their complete cycle of development, and metacyclic (infective) forms were found in large numbers in the salivary glands. From the two *G. morsitans* seven guinea-pigs and a number of mice were infected, either by the bites of the infective tsetse flies or by inoculation of the metacyclic trypanosomes from their salivary glands (Table I). In one of the flies (*G. morsitans*), fed on the resistant variety, the trypanosomes passed through their complete cycle of development, and its salivary glands were found to be swarming with metacyclic forms. From this infective *G. morsitans* five guinea-pigs and a considerable number of mice were infected, either by the bite of the insect or by injection of the metacyclic trypanosomes from its salivary glands (Table I).

The response to the various arsenicals of the fly-transmitted normal strain and that of the fly-transmitted resistant variety were then examined in detail. It was found, as is shown in Tables III and IV, that in neither instance had the passage of the parasite through *Glossina* in any way altered its reaction to arsenicals—that is, the fly-transmitted normal strain was just as sensitive to arsenicals as was its normal parent strain, and the fly-transmitted resistant strain was just as resistant as was its resistant parent strain. In assessing the significance of these results it must be borne in mind that no animal infected with the trypanamide-resistant strain used in these experiments could possibly receive benefit from even maximum tolerated doses of any aromatic compound of arsenic.

CONCLUSION

The experiments afford, in our opinion, unequivocal evidence that the acquired character of "arsenic resistance" in trypanosomes is transmitted unimpaired through the biological cycle of the parasite in *Glossina*, its natural invertebrate host. Apart from its academic and scientific interest, this fact has an obvious bearing on the question of treating sleeping sickness patients in the presence of tsetse fly, and particularly on the prophylactic measure, much favoured by the French, of wholesale atoxylation of patients in their villages by means of itinerant medical organizations.

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CHRONIC PULMONARY TUBERCULOSIS: A NEW CONCEPTION

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When the handling of chronic pulmonary tuberculosis in the mass is considered it will be realized that there has been scarcely any change in our conception of the behaviour of the disease or in our routine treatment within the last twenty years. Collapse therapy has been introduced with most excellent results for the individual case, but with very slight effect on mass results. The improvement in the use and interpretation of x rays has led to earlier diagnosis, and, when intelligently used, to more accurate appraisement of the individual case. But this advance cannot be said to have influenced the accepted conceptions of the disease as much as it should have done, and although the death rate has fallen steadily the expectancy of life for the diagnosed patient has hardly improved. We are still confronted with the fact that, if we take any given batch of patients who are put through the routine treatment, which includes the sanatorium, although they may make a splendid immediate response to treatment, yet if their after-histories are examined we find a small percentage alive and well, another percentage incapacitated or dying, and a large percentage dead.

No one can gainsay the excellent immediate results of sanatorium treatment in such cases as are considered suitable for it on our present standards, and these constitute the bulk of the cases coming up for diagnosis in our hospital out-patient departments and our tuberculosis dispensaries. We must admit that our routine treatment and sanatorium treatment, whatever may be their immediate results, have, *per se*, no specific permanent curative effect on the disease. They may prolong life for a few years in the majority of cases—often useless years—but they afford no protection against relapse and extension of disease. Statistical results prove that whatever successes we do obtain must be ascribed to some other agency. Much excellent work on tuberculosis has been published during the last twenty years, and has been generally accepted as true. But these truths have not been allowed to influence our practical routine treatment of the average case. It is time that they were, and that they should be used to form the basis of a new conception of the disease, and of an attempt to reorganize and improve our routine mass treatment.

SEVEN POSTULATES

I put forward a new conception herewith. It is based on the accepted research work published during the last twenty years. I am building it on seven postulates. Space forbids my recording in this paper the steps by which I have arrived at these, nor would it seem necessary; for, since their acceptance will explain the occurrence of certain well-recognized clinical phenomena, whether true or not, they form to my mind a satisfactory working hypothesis.

1. That after the first infection of the human body, with its resulting "primary focus," be this situated where it may, the first manifestation, or the early lesion, of the adult type of chronic pulmonary tuberculosis is due to a haematogenous deposit of bacilli obtained by the blood stream from the lymphatic system and accompanied by a local allergic tissue reaction. I shall call this a *secondary lesion*. (The term "primary focus" has for so long been accepted as the official title of the